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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EMCH, GREGORY S	
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1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,328	KUAI ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,17 and 22-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,17 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The finality of the last Office action is withdrawn, and new grounds of rejection are set forth below. The amendment filed on 21 September 2009 has been received and entered in full.

Response to Amendment

Claims 1, 3, 8 and 17 have been amended and claims 33-37, 39 and 44-56 have been canceled as requested in the amendment filed on 21 September 2009. Following the amendment, claims 1-12, 17 and 22-25 are pending in the instant application.

Election/Restrictions

In the reply filed on 21 September 2009, applicants request rejoinder of claims 3-7, 9, 10, 17 and 22-25. Applicants assert that claims 3-4 and 6-9 comprise TRCP1 (the elected species) in addition to non-elected species and that claims 5, 10, and 24 and all claims depending directly or indirectly from claim 1, comprise the elected species of TRCP1 in addition to the non-elected species. Thus, applicants request that these claims be rejoined into the elected invention.

Applicants' arguments have been fully considered and are found persuasive. The elections of species requirements set forth on pp.4-8 of the restriction requirement dated 27 August 2007 are hereby vacated. Claims 3-7, 9, 10, 17 and 22-25 are hereby rejoined for examination on the merits. Note however that the restriction between Groups I-X set forth on pp.1-4 of the restriction requirement dated 27 August 2007 is

maintained. Applicants timely traversed the restriction requirement between Groups I-X in the reply filed on 05 October 2007.

Claims 1-12, 17 and 22-25 are under examination in the instant office action.

Withdrawn Rejections

The rejection of claims 1, 2, 8, 11 and 12 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement is withdrawn in response to the amendment to the claims to delete "or a functional variant thereof."

However, upon further consideration, a new ground(s) of rejection is made as set forth below.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 17 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the

amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

Regarding the nature of the invention, the claims are directed to isolated, purified or recombinant protein complexes comprising tumor necrosis factor-alpha (TNF), a TNF receptor (TNFR) and a TRCP1 polypeptide. Dependent claims specify that the complex further comprises a RasGAP3 polypeptide, an NF-κB polypeptide activating kinase (NAK) polypeptide, a TRCP2 polypeptide, TRADD, TRAF2 and/or TRAP2. Thus, the claims are directed to a protein complex that comprises various combinations of proteins, all of which are part of TNF signal transduction cascades, including a complex that comprises all members of a TNF signal transduction cascade.

The specification teaches that the effects of TNF ligands and receptors are varied and influence numerous functions, both normal and abnormal, in the biological processes of the mammalian system and that there is a clear need, therefore, for identification and characterization of protein complexes comprising such receptors and ligands, which influence biological activity, both normally and in disease states (paragraph [0005]). The specification teaches that prophetic uses of protein complexes of the invention include assays for identifying test compounds that inhibit or potentiate the stability of a protein complex of the invention. For example, it is taught that an assay comprises: forming a reaction mixture including TNF, TNFR, and at least one polypeptide selected from the group consisting of: NAK, RasGAP3, TRCP1, and

TRCP2, and a test compound; and detecting the presence of TNF or TNFR in the complex. Here, a change in the presence of TNF or TNFR in the complex in the presence of the test compound, relative to the presence of TNF or TNFR in the complex in the absence of the test compound, indicates that said test compound potentiates or inhibits the stability of said complex [0011]. It is taught that a two-hybrid system can be used to screen for interaction between the polypeptides in the presence and absence of a test compound [0014] and that in certain embodiments, the invention provides methods for modulating, in a cell, a protein complex comprising a first protein, a second protein and a third protein, wherein said first protein is TNF, said second protein is TNFR and said third protein is selected from the group consisting of: NAK, RasGAP3, TRCP1, and TRCP2. Here, the method comprises administering to said cell a compound capable of modulating said protein complex [0016]. The specification provides one example (Example 2), which teaches that the binding of certain polypeptides encompassed by the claims was measured by western blotting [0166 and 0177]. Specifically, it is stated that the ligand-induced binding of the TNFR1 with NAK, TRAF2, or TRADD in a time-dependent manner is shown in FIG. 22. Here, myelomonocytic leukemia cells (U937 cells) were incubated with FLAG-tagged TNF for 2, 5, 10, 20, or 30 minutes or left untreated. Cells were lysed by 0.5% Triton and the cell lysates were immunoprecipitated with an anti-FLAG antibody (M2) conjugated to the Sepharose beads. The immunoprecipitated complex was washed, eluted with protein sample buffer, and then resolved on 4-12% SDS-PAGE gels. The presence of NAK in the TNF receptor complex was detected by western blotting. Similarly, cells lysates

were immunoprecipitated with an anti-TNFR1 antibody. The association of the TNF receptor with NAK, TRAF2, or TRADD was subsequently detected by western blotting with antibodies against NAK, TRAF2, or TRADD.

Regarding the state of the art, the prior art is silent with regards to isolating members of cellular signal transduction cascades which are do not normally bind to each other *in vivo* and providing them in protein complexes for further analysis. That is, independent claim 1 is drawn to an isolated, purified or recombinant protein complex comprising tumor necrosis factor-alpha (TNF), a TNF receptor and a TRCP1 polypeptide. Bour et al. (J Biol Chem. 2001 May 11;276(19):15920-8. Epub 2001 Feb 16) teaches that TRCP1 is a downstream member of a TNF signal transduction cascade, which does not directly bind to TNF or TNFR, but instead binds to other proteins in the cascade (i.e. IκB or Vpu; see p.15926, Figure 6). Given that TNF, TNFR and TRCP do not directly bind to each other at one time, the skilled artisan would not know how to use a protein complex that consists of said proteins. Regarding claims which require additional proteins be present in the protein complex, (e.g. claim 8, which requires the complex of claim 1, further comprising at least one polypeptide selected from: TRADD, TRAF2, TRAP2; claim 9 which requires TNF, TRCP1, NAK, TNFR1, TRAF2 and TRADD; or claim 10, which requires TNF, TNFR, NAK, RasGAP3, TRCP1, TRCP2, TRADD, TRAF2, and TRAP2), there art is again silent with regards to all of these protein being present in a single complex and is silent with regards to any potential use of such a complex. Rather, the art indicates that these proteins bind to each other in an intermediate fashion and do not all bind to each other at the same time

(see e.g. Heyninck et al. Mol Cell Biol Res Commun. 2001; Cite No. CI on IDS dated 13 June 2005, pp.260-261, figures 1 and 2). Thus, the art is silent with regards to a potential use of the claimed invention.

Regarding the level of skill in the art, it is well known that the level of skill in the protein engineering arts is high. However, given that the art teaches that the proteins encompassed by the claims do not bind to each other all at the same time and given that the art is silent with regards to a potential use of such a complex as is claimed, the invention is unpredictable.

Therefore, the quantity of experimentation to achieve the results required by the claims is deemed to be quite large. In general, the claimed polypeptides can each be separately generated; however, the use of the claimed protein complexes (which require different combinations of proteins that have not been shown as capable of binding to each other) are absent from the literature. The specification does not disclose how such complexes are to be used other than by generically subjecting them to a test compound and determining how the test compound affects the complex. The specification does not provide a true nexus between the claimed complex and screening assays for treatment of disease, for example. Indeed, the specification asserts that compounds can be identified for treatment of disease. As set forth above, the specification teaches that an assay of the invention comprises (i) forming a reaction mixture including TNF and/or TNFR, at least one polypeptide selected from the group consisting of: NAK, RasGAP3, TRCP1, and TRCP2, and a test compound; and (ii) detecting the association between the TNF or TNFR and said at least one polypeptide.

Here, a change in the association between TNF or TNFR and said at least one polypeptide in the presence of the test compound, relative to the association in the absence of the test compound, indicates that said test compound potentiates or inhibits the assembly, stability or function of said complex, and the specification asserts that the test compound may be useful for treating disease [0012, 0136]. Further outcome measures include determining a change in the level of the complex, the level of TNF or the level of TNFR or determining a change in the signaling enzymatic activity of the complex [0013]. Methods for treating a TNF related disorder by administering an effective amount of a compound that inhibits the interaction of TNF or TNFR with a polypeptide selected from the group consisting of: NAK, RasGAP3, TRCP1, and TRCP2 are disclosed [0014 and 0018]. Further, methods to identify a candidate modulator of inflammation or apoptosis are disclosed, comprising forming a mixture comprising a TRCP1 or TRCP2 polypeptide or a variant polypeptide thereof, and a test compound; and (ii) measuring the interaction between the TRCP1 or TRCP2 polypeptide or the variant and the test compound; wherein a test compound that interacts with the TRCP1 or TRCP2 polypeptide or the functional variant thereof is a candidate modulator of inflammation or apoptosis [0019, 0020]. But these assay methods are not on point to using the claimed complex to identify a treatment compound; these are only on point to measuring the ability of a compound to inhibit the interaction of TNF OR TNFR with ONE of NAK, RasGAP3, TRCP1 or TRCP2 or to measuring the ability of a compound to interacts with the TRCP1 or TRCP2 polypeptide to identify a potential treatment compound. Furthermore, since the art teaches that the claimed polypeptides do not

bind to each other all at the same time, assay methods which include said polypeptides are assumed to be inoperable. Therefore, the skilled artisan must determine, through trial and error analysis, ways to use the claimed invention.

Due to the large quantity of experimentation necessary to achieve a use of the claimed protein complexes, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art, the unpredictability of the claims, undue experimentation would be required of the skilled artisan to use the claimed invention.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Bour et al. (J Biol Chem. 2001 May 11;276(19):15920-8. Epub 2001 Feb 16, referred to above) teaches the polypeptides recited by independent claim 1 together in one figure (i.e. TNF, TNFR and TRCP1, see p.15926, Figure 6) but does not teach an isolated, purified or recombinant protein complex comprising all of the polypeptides. Given that the claims are not considered enabled, this reference also does not qualify as prior art under 35 U.S.C. 103(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

Gregory S. Emch
Patent Examiner
Art Unit 1649
02 November 2009

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
November 4, 2009